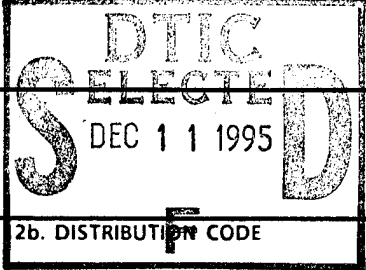
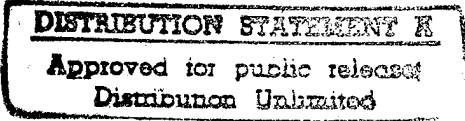


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6. AUTHOR(S) Charles G. Cochrane, M.D.					
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13. ABSTRACT (Maximum 200 words) A peptide-containing pulmonary surfactant has been developed, called KL ₄ -Surfactant. Assessment of activity and safety has been performed successfully in preterm subhuman primates and in 47 preterm human infants (IND #40,287). This synthetic surfactant is now being tested in Adult human RDS.					
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RESEARCH FINAL REPORT

Title: Clinical Studies of Synthetic Peptide-Containing Pulmonary Surfactant in Patients with Adult Respiratory Distress Syndrome

Principal Investigator: Charles G. Cochrane, M.D.

Grant/Contract No: N00014

Period of Performance: 08/01/94 - 07/31/95

Major Accomplishments:

Mechanisms of function of pulmonary surfactant protein

Of the three major proteins incorporated in pulmonary surfactant, protein B (SP-B), when dispersed with phospholipids, was found to impart the greatest counteraction to surface tension. The structural features of SP-B responsible for this function were found to be hydrophobic stretches of amino acids with intermittent basic hydrophilic residues. Peptides that mimicked SP-B were synthesized consisting of stretches of leucines with intermittent lysines or arginines. Data utilizing amino acid substitution and Raman spectroscopy, revealed that the basic residues form a charge interaction with the hydrophilic head groups of the phospholipids, providing inter- and intra-molecular ordering of the phospholipid molecules and lateral stability to the phospholipid monolayer. These peptides, dispersed in dipalmitoyl PC and palmitoyl-oleoyl PG, called KL₄-surfactant, induced strong surfactant function. When such dispersions were administered to 130-day gestation rhesus monkeys, that otherwise suffered failing pulmonary function, a marked improvement in function occurred. Over fifty infant monkeys, so treated, showed an increase in arterial/alveolar O₂ ratio to the normal range, and excellent expansion of the lungs, as opposed to no improvement in 6 monkeys receiving phospholipid without protein or peptide.

Studies in human infants: IRDS

Similarly, with FDA approval of the use of KL₄-surfactant for use in human premature infants (IND #40,287), 38 human infants have been treated in a Phase I/II study. All have responded with an improvement of pulmonary function, often dramatically, as noted in the accompanying figure. The IRDS clinical trial has, to date, shown no evidence of toxicity, confirming preclinical studies in animals, and has revealed marked efficacy in terms of pulmonary function. There have been no RDS-related deaths.

Clinical trials have been started in adults with ARDS in August 1995.

Anti-inflammatory effects of KL₄-surfactant

While the administration of exogenous surfactant in RDS may induce expansion of atelectatic lung and improvement of pulmonary function which may, in turn, improve oxygenation and perfusion in other failing organs, the KL₄-surfactant has also been found to have an anti-inflammatory effect. Collaborative studies with Drs. Roger Spragg and Robert Smith have indicated that KL₄-surfactant inhibits the oxidative burst of human neutrophils. Stimulation of neutrophils with phorbol esters or N-formylated peptides in the presence or absence of varied concentrations of KL₄-surfactant have revealed 10-100 fold diminished formation of O₂⁻ in the presence of the surfactant. This is not explained by diminished binding of the stimulants; and the inhibition occurs at a position of the oxidase pathway distal to Ca²⁺ mobilization. The effect of surfactant on the various cytoplasmic and membranous compounds of the oxidase system are under current investigation. We have previously published on the inhibition in vivo of surfactant administration on leukocytic oxidant and protease generation. In addition, IL-8 levels in bronchoalveolar lavage fluid of ARDS patients is decreased following surfactant administration. The anti-inflammatory capacity of the KL₄-surfactant is therefore of significance in the treatment of ARDS and merits further study. The potential anti-inflammatory effects will constitute a central feature of our ARDS clinical trial.

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